well as our own experience, demonstrate the reluctance of physicians to up-titrate nitroglycerin doses, especially in patients being treated without hemodynamic monitoring.[1] Our findings also reflect the temporary nature of the nitrate-induced hemodynamic effect because of the early development of tolerance[8,9] Attenuation of effect with continuous vascular exposure to nitrates has recently been suggested to be caused by increased production of oxygen-free radicals, which leads to decreased bioavailability of nitrate-derived nitric oxide[10,11] and a negative effect on the function of nitric oxide synthase, the enzyme responsible for endothelial control of vascular tone.[12,13]

This study represents a subgroup analysis of data from 1 individual center participating in the VMAC study. As such, the results are limited by a relatively small sample size and the derivative experience. In addition, although the maximum mean dose of nitroglycerin used at this site was high relative to that for all sites participating in the VMAC study, even higher doses may be used in clinical practice. Higher doses of nitroglycerin may have similar or different clinical outcomes.

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Meta-Analysis of Effectiveness or Lack Thereof of Angiotensin-Converting Enzyme Inhibitors for Prevention of Heart Failure in Patients With Systemic Hypertension

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We undertook a meta-analysis of large, randomized controlled trials in hypertensive subjects that compared angiotensin-converting enzyme (ACE) inhibitors with different classes of antihypertensive drugs. Compared with subjects randomized to drugs different from ACE inhibitors, those treated with ACE inhibitors did not show a different risk of congestive heart failure (CHF) (odds ratio 1.03, 95% confidence interval 0.96 to 1.12, p = 0.407). The degree of protection from CHF associated with the use of ACE inhibitors showed a nonsignificant trend to increase with age and the degree of blood pressure control. Thus, the hypothesis that ACE inhibitors are superior to other antihypertensive drugs for prevention of CHF in hypertension remains unproven.

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Angiotensin-converting enzyme (ACE) inhibitors improve symptoms and prolong survival in patients with congestive heart failure (CHF). In a meta-analysis of 7 large studies in patients with CHF or left ventricular dysfunction, ACE inhibitors were associated with a significant decrease in a composite of death, myocardial infarction, and hospital admission for patients with CHF (odds ratio [OR] 0.72, 95% confidence interval [CI] 67 to 78).[1] However, although the benefits of ACE inhibitors in patients with CHF are well established, their potential value for

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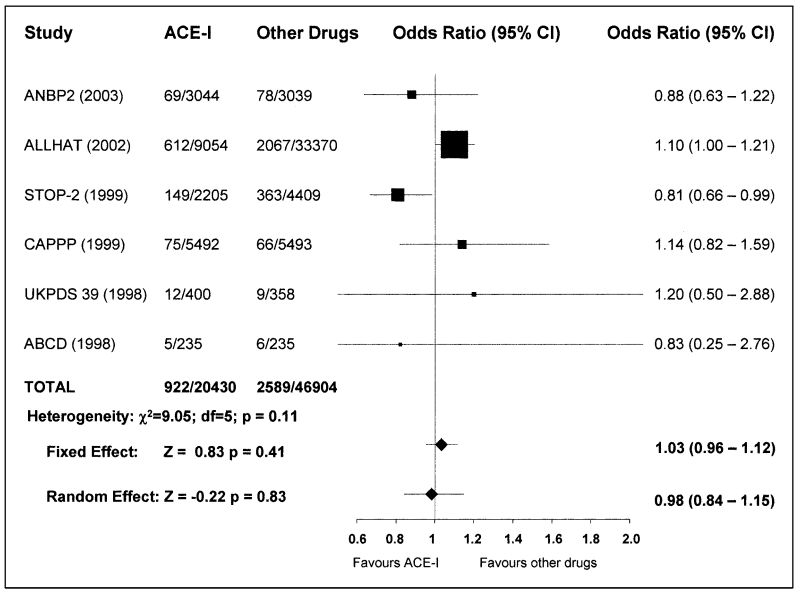

FIGURE 1. Heart failure events associated with ACE inhibitors (ACE-I) and drugs with different mechanisms of action in patients with essential hypertension. ABCD = Appropriate Blood Pressure Control in Diabetes; ANBP2 = Second Australian National Blood Pressure Study Group; CAPPP = Captopril Prevention Project; STOP-2 =Swedish Trial in Old Patients with Hypertension-2 study; UKPDS = UK Prospective Diabetes Study Group.

primary prevention of CHF in patients with hypertension is still unclear. By blunting the renin–angiotensin system over the long term, ACE inhibitors might prevent or delay progression of myocardial fibrosis and structural disarray in the hypertensive heart,[2,3] and, thus may have potential valuable implications for the prevention of CHF.

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We undertook a meta-analysis of major clinical trials in hypertension that compared ACE inhibitors with different antihypertensive drugs in subjects with primary hypertension. We tested whether treatment with ACE inhibitors was associated with a lower risk of CHF. We selected only the studies that met all of the following prespecified criteria: (1) publication in a peer-reviewed journal indexed in MEDLINE; (2) inclusion of patients with a clinical diagnosis of essential hypertension; (3) occurrence of CHF as a prespecified end point during follow-up; (4) definition of CHF events in the single studies; (5) assessment of blood pressure at baseline and at follow-up visits; (6) randomized controlled design; (7) follow-up of $\geq$2 years; and (8) sample size $\geq$100 subjects.

Studies were identified through MEDLINE using research methods filters[4] with publication dates before June 30, 2003. The final search identified 6 studies[5–11] that fulfilled the inclusion criteria. Two of these studies had enrolled patients with hypertension and type 2 diabetes.[8,9] The Analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) included the reports published in 2000[6] and 2002[7] to allow an assessment of the effects of doxazosin[6] in addition to other treatments.[7] For all studies, we accepted the definition of CHF events reported in the individual reports. All outcome results were reported on the basis of an intention-to-treat approach.

The reference group was composed of patients randomly assigned to antihypertensive drugs different from ACE inhibitors. The OR and 95% CI for CHF were calculated separately for each of the 6 studies according to fixed- and random-effect models. The assumption of homogeneity between patient studies was tested using the Zelen's test. Analyses were performed using the Comprehensive Meta-Analysis software (Biostat, Englewood, New Jersey). We used the SPSS 11.0 statistical package (SPSS Inc., Chicago, Illinois) to correlate the ORs of treatment with ACE inhibitors versus other antihypertensive drugs with the corresponding differences in achieved systolic blood pressure. For these calculations, the regression lines were weighted by the inverse of variance of patient ORs.

Table 1 lists the main characteristics of the clinical trials. All of the trials—except the Appropriate Blood Pressure Control in Diabetes[9] study, which enrolled patients affected by type 2 diabetes with or without hypertension—were conducted in subjects with hypertension. For the purpose of the present analysis, we included only the cohort of subjects with hypertension. The age of subjects ranged from 52 to 73 years, and male gender prevailed (range 33% to 55%). The duration of follow-up ranged from 4.1 to 8.4 years. At randomization, none of the subjects had clinical evidence of CHF in most studies,[4–8] whereas 0.3% of subjects in 1 study[11] and 1.9% of subjects in another study[10] had a previous diagnosis of CHF.

Overall, there were 3,511 new cases of CHF: 922 among the subjects randomized to ACE inhibitors and 2,589 among the subjects randomized to other antihypertensive drugs. The risk of CHF did not differ between subjects randomized to receive ACE inhibitors and subjects randomized to receive different classes of antihypertensive drugs (fixed effect: OR 1.03, 95% CI 0.96 to 1.12; p = 0.407; random effect: OR 0.98, 95% CI 0.84 to 1.15; p = 0.83) (Figure 1). Because of its large sample size, ALLHAT[6,7] exerted a major influence on the overall meta-analysis estimate. For example, the OR for CHF in the lisinopril groups compared with the other non-ACE groups in ALLHAT was 1.10 (95% CI 1.00 to 1.21) with a p value bordering on significance (p = 0.050). The percentage weight contributed by ALLHAT to the overall metaanalysis was 68.7%.

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In patient studies, the degree of protection from CHF, expressed in terms of OR in the ACE inhibitor group compared with the other group, showed a nonsignificant trend to increase with age (R^2 = 0.38) and a nonsignificant trend to decrease with achieved sys-

TABLE 1 Characteristics of Trials Comparing Angiotensin-Converting Enzyme (ACE) Inhibitors With Different Antihypertensive Drugs

Characteristics	UKPDS 39[8]	ABCD[9]	STOP-2[10]	CAPPP[11]	ALLHAT[6,7]	ANBP2[5]
Yr of publication	1998	1998	1999	1999	2000, 2002	2003
Diabetes mellitus	+	+	−	−	−	−
Demographic characteristics						
No. of patients (ACE-I/others)	400/358	235/235	2,205/4,409	5,492/5,493	9,054/24,316	3,044/3,039
Age in years (ACE-I/others)	56.3/56.0	57.7/57.2	76.1/75.9	52.4/52.7	66.9/66.9	72/72.9
% Men (ACE-I/others)	51/57	50/47	34/33	55/52	46/47	50/48
Type of treatment						
ACE-I	Captopril	Enalapril	Enalapril/lisinopril	Captopril	Lisinopril	Enalapril
Reference drugs	Atenolol	Nisoldipine	β blockers/diuretic/ CCB	β-blockers/diuretic	Amlodipine/chortalidone/ doxazosin	Diuretics
Add-on drugs	Furosemide, nifedipine, methyldopa, prazosin	Metoprolol, diuretics	Diuretics, β blockers	Ca-antagonists, diuretics	Atenolol, idralazine, resrpine, clonidine	β-blockers, Ca-antagonists, α-blockers
No. of CHF events during follow-up ACE-I/others	12/9	5/6	149/363	75/66	612/2,067	69/78
Systolic BP at baseline in mm Hg (ACE-I/others)	159/159	156/155	194/194	162/160	146/146	167/168
Difference in achieved systolic BP in mm Hg (ACE-I minus others)	−1	−1	−0.5	−3	−1.3	1
Follow-up (yrs)	8.4	5.6	4.5	6.1	4.9	4.1

ACE-I = angiotensin converting enzyme inhibitor; BP = blood pressure; CCB = calcium channel blocker; CHF = congestive heart failure; other abbreviations as in Figure 1.

tolic blood pressure ($R^2 = 0.33$). These associations were not statistically significant, possibly because of the limited numbers of reviewed studies. However, these trends raise the hypothesis that ACE inhibitors may provide greater potential benefits for CHF prevention in elderly hypertensive subjects as well as in those with a better control of systolic blood pressure who are using treatment.

Our results extend those of a recent meta-analysis by Staessen et al,[12] who limited their assessment to the effects of ACE inhibitors versus conventional drugs (diuretics and/or β blockers) in some of the trials considered in this report. The risk of CHF did not differ between subjects randomized to receive ACE inhibitors and subjects randomized to receive diuretics and/or β blockers ($p = 0.64$).[12] Notably, our overview allows us to extend these conclusions to all antihypertensive drugs that are different from ACE inhibitors, including calcium-channel blockers and α-1 blockers.

Although there was no significant heterogeneity across the studies (chi-square 9.05; degree of freedom 5; $p = 0.11$), diagnoses of CHF were not uniform. In 5 studies,[5,8,9–11] adjudication of CHF events was made by an independent end-point committee whose members were blinded to the treatment group. In all of these studies, adjudication of CHF required subject admission to the hospital. In 1 study,[7] diagnosis of CHF was left up to individual investigators, with 1.9% of CHF events in that study[7] reviewed by a committee.[13]

The mean duration of follow-up, <5 years in half of the studies, may have been too short to disclose a protective effect of long-term ACE inhibition on the prevention of CHF. In addition, ACE inhibitors may have failed to fully suppress the activity of the renin–angiotensin system during long-term treatment because of activation of other angiotensin-II–generating pathways.[14,15] Angiotensin II reactivation and failure of aldosterone suppression have been found in up to 38% of patients with CHF taking an ACE inhibitor.[14] These phenomena have been ascribed to poor compliance with therapy in patients with low levels of ACE inhibition or to activation of alternative angiotensin-II–generating pathways in those with low ACE and high angiotensin II concentrations.[14] The frequency of angiotensin II reactivation and failure of aldosterone suppression in apparently healthy subjects with essential hypertension treated with ACE inhibitors are unknown.

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